Epidemiology of Viral Gastroenteritis in Iran

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When comparing BMD with Vitek 2, only 44 (21%) had different MIC values with the vast majority (95%) different by only 1-well dilution. Overall, Vitek 2 results were more consistent with BMD, while standard Etest appeared to overestimate MICs when compared with the standard method of BMD.

Clinical patient data were available for 187 patients (63 MRSA and 124 MSSA). There were no differences in median length of hospital stay, median hospital cost or all-cause mortality when comparing patients infected with a staphylococcal isolate with an MIC <1 μg/mL compared with those with an MIC ≥1 μg/mL or when comparing patients with MSSA versus MRSA bacteremia.

DISCUSSION

In the adult population, the trend during 2000–2005 toward increasing vancomycin MIC values for *S. aureus*,[2,10] so-called "MIC creep," has led to the concern that vancomycin may no longer be appropriate to treat invasive staphylococcal infection in adults where the MIC is ≥2 μg/mL. Furthermore, the increase in vancomycin MICs has been associated with worse outcomes in adults with invasive *S. aureus* disease.[4,5] We did not observe a similar trend in our pediatric population during the study period. Our data are consistent with other reports in which a significant vancomycin MIC increase in pediatric populations was not demonstrated.[6,7] There is not a clear explanation for the difference in MIC trends between children and adults. However, it may be related to differences in vancomycin usage (both frequency of use and dosing strategies) in children and adults leading to differences in resistance patterns of *S. aureus*. Our study is the first to specifically evaluate all blood isolates during a specified period.

We also evaluated the prevalence of heterogeneous vancomycin-intermediate *S. aureus* in our pediatric population with invasive MRSA. Evaluation of the presence of vancomycin heteroresistance is challenging as there is a lack of standardized methodology for identification and the gold standard, population analysis profile to vancomycin exposure curve ratio (PAP-AUC), can be labor-intensive and is typically unavailable in clinical laboratory settings. We used the Etest GRD method as a screening test to detect vancomycin heteroresistance for all MRSA isolates in our population. This method has demonstrated relatively high specificity and sensitivity when compared with PAP-AUC, suggesting that it may be an adequate screening test.[11] However, confirmation of positive tests by PAP-AUC is warranted. Although no vancomycin heteroresistance was identified among our isolates, observations should be confirmed in other pediatric populations because of the potentially associated clinical complications and poor outcomes reported in adult cases.

Storage of *S. aureus* isolates can potentially impact vancomycin susceptibility results and is a recognized limitation of this study. Furthermore, results over a more extensive study period may potentially demonstrate an increasing trend in vancomycin MICs. Finally, a larger sample size may be required to detect heteroresistance.

In our study, vancomycin MIC results varied across testing methods, with the standard Etest resulting in a higher value 94% of the time when compared with BMD. This could be problematic in clinical care as a falsely elevated vancomycin MIC may deter a clinician from using vancomycin in a scenario in which it would otherwise be the preferred first-line therapy. Therefore, it is essential for clinicians to be aware of the testing method used for susceptibility testing in their institution and consider MIC results in light of the method when selecting vancomycin as the preferred antimicrobial agent.

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REFERENCES

1. Gerber JS, Coffin SE, Smathers SA, et al. Trends in the incidence of methicillin-resistant *Staphylococcus aureus* infection in children's hospitals in the United States. *Clin Infect Dis*. 2009;49:65–71.
2. Steinkraus G, White R, Friedrich L. Vancomycin MIC creep in non-vancomycin-intermediate *Staphylococcus aureus* (VISA), vancomycin-susceptible clinical methicillin-resistant *S. aureus* (MRSA) blood isolates from 2001-05. *J Antimicrob Chemother*. 2007;60:788–794.
3. Kullar R, Davis SL, Levine DP, et al. Impact of vancomycin exposure on outcomes in patients with methicillin-resistant *Staphylococcus aureus* bacteremia: support for consensus guidelines suggested targets. *Clin Infect Dis*. 2011;52:975–981.
4. Soriano A, Marco F, Martínez JA, et al. Influence of vancomycin minimum inhibitory concentration on the treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *Clin Infect Dis*. 2008;46:193–200.
5. Lodise TP, Graves J, Evans A, et al. Relationship between vancomycin MIC and failure among patients with methicillin-resistant *Staphylococcus aureus* bacteremia treated with vancomycin. *Antimicrob Agents Chemother.* 2008;52:3315–3333.
6. Mason EO, Lamberth LB, Hammerman WA, et al. Vancomycin MICs for *Staphylococcus aureus* vary by detection method and hae subtly increased in a pediatric population since 2005. *J Clin Microbiol.* 2009;47:1628–1630.
7. Zheng X, Qi C, Arrieta M, et al. Lack of increase in vancomycin resistance of pediatric methicillin-resistant *Staphylococcus aureus* Isolates from 2000 to 2007. *Pediatr Infect Dis J*. 2010;29:882–884.
8. Clinical and Laboratory Standards Institute. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically: M07-A8*. Wayne, PA: Clinical and Laboratory Standards Institute; 2009.
9. Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing: 19th Informational Supplement: M100-S19*. Wayne, PA: Clinical and Laboratory Standards Institue; 2009.
10. Wang G, Hindler JF, Ward KW, et al. Increased vancomycin MICs for *Staphylococcus aureus* clinical isolates from a university hospital during a 5-year period. *J Clin Microbiol*. 2006;44:3883–3886.
11. Leonard SN, Rossi KL, Newton KL, et al. Evaluation of the Etest GRD for the detection of *Staphylococcus aureus* with reduced susceptibility to glycopeptides. *J Antimicrob Chemother*. 2009;63:489–492.

EPIDEMIOLOGY OF VIRAL GASTROENTERITIS IN IRAN

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Abstract: Viruses are prominent causative agents of acute gastroenteritis in children <5 years of age per year.[1] In the present review, all viral gastroenteritis studies in Iran were assessed, and the mean prevalences of rotaviruses, noroviruses, enteric adenoviruses, sapoviruses and astroviruses associated with acute gastroenteritis were 39.9%, 6%, 5.7%, 4.2% and 2.7%, respectively. In 2 studies, human bocavirus and human parechovirus were detected in 21.8% and 23.7% of children with acute gastroenteritis, respectively.

Key Words: viral gastroenteritis, prevalence, Iran

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TABLE 1. Detection Rates of RVs, NoVs, EAdVs, SaVs and AstVs in Children With Acute Gastroenteritis in Iran Between 1986 and 2011

Viral Agents	Number of Samples Tested	Positivity Rate, n (%)	Number of Studies	Year	References
RVs	13,383	5335 (39.9)	22	1986–2011	4–7
EAdVs	3539	200 (5.7)	9	1999–2010	4,8–15
NoVs	3028	182 (6.0)	5	2006–2010	4, 15–18
SaVs	289	12 (4.2)	3	2006–2009	16,19,20
AstVs	3629	98 (2.7)	5	2002–2010	4,14,21–23

RVs indicates rotaviruses; EAdVs, enteric adenoviruses; NoVs, noroviruses; SaVs, sapoviruses; AstVs, astroviruses.

Diarrhea is an important symptom of most enteric infections that are most frequent in children <5 years of age. In 1992, Bern et al[1] published a review manuscript of studies from 1980s and reported 3.3 million deaths. They estimated 2–3 episodes of diarrhea per child of <5 years of age every year in developing countries. In 2003, Kosek et al[2] published a review of the burden of diarrheal disease from reports between 1992 and 2000. They reported 3.2 episodes per child <5 years of age per year in developing countries and also estimated 2.5 million deaths (range: 2.1–4.7 million), which was less than that in previous studies. In addition, the mortality rate of diarrhea disease was 4.9 per 1000 per year in the 1990s, which was decreased compared with reported previous studies. Bern et al[1] reported 13.6 and 5.6 per 1000.

Agents that were recognized to cause diarrheal disease include bacteria, parasites and viruses. In developing countries, rotaviruses (RVs) are responsible of approximately 20% of diarrhea-related deaths in children <5 years of age. Noroviruses (NoVs) and Sapoviruses (SaVs) of the Caliciviridae family also cause acute gastroenteritis (AGE). Currently, NoVs as emerging viruses are the most important cause of AGE, particularly in countries after introduction of universal RV vaccination. Many studies have shown that SaVs are important in outbreaks of sporadic gastroenteritis in children <5 years of age. Enteric adenoviruses (EAdVs), serotypes 40 and 41, are also associated with AGE. The frequency of EAdV-associated gastroenteritis varies considerably in the various studies and locations. Astroviruses (AstVs) also increasingly detected as another viral causing of gastroenteritis which reported in up to 10% of sporadic gastroenteritis.[3] Moreover, toroviruses and coronaviruses of the Coronaviridae family, human parechoviruses and Aichiviruses of the Picornaviridae family, and human bocavirus (HBoVs) of the Parvoviridae family are other viruses, which have been found to be associated with AGE.

Through improvement of the safety of drinking water and the disposal of sewage, the rate of nonviral gastroenteritis infections has decreased. Detection and management of viral AGE are considered high priority for the healthcare system, inlcuding Iran. In this review, all viral gastroenteritis studies in Iran were assessed to analyze the infection rate and association with enteric viruses.

METHODS

For this review, all published viral gastroenteritis studies from Iran were obtained by searches of Medline, PubMed and National databases. Search key words included: Viral gastroenteritis, diarrhea, Iran, rotavirus, norovirus, adenovirus, astrovirus, sapovirus, parechovirus and bocavirus. Overlapping data were excluded.

RESULTS

Data analysis of 22 gastroenteritis studies[4–7] attributable to rotavirus estimated that prevalence of RV infection was 39.9% (Table 1). EAd40 and AAd41 viruses were detected in 5.7% of the stool samples in 9 published studies[4,8–15] (Table 1). For NoVs and SaVs, positivity rates were on average 6.0% and 4.2% from 5[4,15–18] and 3 studies,[16,19,20] respectively. The prevalence of AstVs was 2.7% on average (5 studies)[4,14,21–23] (Table 1). Another observation was that age and seasonal patterns of AGE due to virus infections in Iran were similar to each other. Viral infection occurred most often in children <2 years of age and during the cooler months.

In 2010, Nadji et al[24] reported HBoVs isolation from 21.8% children with AGE. In 2012, Ghazi et al[25] also showed that the incidence of human parechovirus 1 in children with AGE in Iran was 23.7%.

DISCUSSION

Considering that there have been few reports about burden of viral AGE in Iran, this review provides helpful information about frequency and circulation of viruses causing childhood AGE. RVs, NoVs, AdVs, SaVs and AstVs were all found to be involved as causes of AGE as well as human parechoviruses and HBoV.

Rotaviruses were the most prevalent viral agent causing AGE, consistent with findings in other regions in the world before the introduction of the RV vaccine.[26] NoVs have been shown to be responsible for 70–90% of AGE outbreaks in Europe and the United States, respectively.[18] The prevalence of NoV in Iran was 6.0% which is close to data reported from neighboring countries such as Pakistan.[18] However, the prevalence of NoV in some countries such as India, Iraq, Taiwan, Nicaragua, Brazil and Italy was 12–48%,[18] ie higher than in Iran. The detection rate of SaVs was not as high as that of NoVs in Iran, but it was consistent with rates in studies of other parts of the world.[18] EAdVs were responsible for 5.7% of AGE in children which is much lower than in Nigeria and close to that of epidemiologic reports of adenovirus detection in Brazil, Indonesia, Singapore and China.[26] AstVs as cause of AGE in children which have a prevalence rate of 1.4–8.6% in different reports, but higher rates in Japan and Central America.[26] In Iran, the prevalence of AstV was estimated to be 2.7%, similar to recent reports from Venezuela and Taiwan.[26] In summary, this data analysis suggests that SaVs and AstVs are minor causes of AGE in children compared with RVs, NoVs and EAdVs.

In 2 studies, HBoV and human parechovirus 1 were detected in 21.8% and 23.7% of children with AGE, respectively. These reports were accordance to previous studies,[26] but they need to confirm by further studies.

Overall, most studies assessed in this review have investigated for only a single virus or a limited range of viruses. Therefore, the true prevalence of viruses as cause of AGE and the real burden of viral AGE in Iran remain to be identified in carefully planned prospective studies with appropriate control groups. Furthermore, genotyping should be carried out in such a study to identify the most frequent types of the different viruses responsible for the clinical burden of AGE in children in Iran.

REFERENCES

1. Bern C, Martines J, de Zoysa I, et al. The magnitude of the global problem of diarrhoeal disease: a ten-year update. *Bull World Health Organ*. 1992;70:705–714.

2. Kosek M, Bern C, Guerrant RL. The global burden of diarrhoeal disease, as estimated from studies published between 1992 and 2000. *Bull World Health Organ*. 2003;81:197–204.
3. Glass RI, Noel J, Mitchell D, et al. The changing epidemiology of astrovirus-associated gastroenteritis: a review. *Arch Virol Suppl*. 1996;12:287–300.
4. Najafi A, Najafi S, Vahdat K, et al. Importance of viral pathogens in children with acute gastroenteritis in the south of Iran. *Ann Saudi Med*. 2013;33:124–129.
5. Shoja Z, Jalilvand S, Mokhtari-Azad T, et al. Epidemiology of cocirculating human rotaviruses in Iran. *Pediatr Infect Dis J*. 2013;32:e178–e181.
6. Najafi A, Kargar M, Kargar M, et al. Burden and typing of rotavirus group a in children with acute gastroenteritis in shiraz, southern Iran. *Iran Red Crescent Med J*. 2012;14:531–540.
7. Jadali F, Karimi A, Fallah F, et al. A survey on rotavirus associated diarrhea in 5 main cities of Iran. *Arch Pediatr Infect Dis*. 2012;1:23–26.
8. Rezaei M, Sohrabi A, Edalat R, et al. Molecular epidemiology of acute gastroenteritis caused by subgenus F (40, 41) enteric adenoviruses in inpatient children. *LabMedicine* 2012;43:10–15.
9. Nakhaei Sistani R, Sadeghizadeh M, Saderi H, et al. Detection of types 40 and 41 adenoviruses in stool samples of diarrheal children by solid phase PCR. *Iran J Biotechnol*. 2007;5:42–47.
10. Modarres S, Jam-Afzon F, Modarres S. Enteric adenovirus infection in infants and young children with acute gastroenteritis in Tehran. *Acta Med Iranica* 2006;44:349–353.
11. Hamedi A, Sadeghian A, Syedi J. Incidence of adenovirus diarrhea in children under 6 years referred to the pediatric emergency and clinic of Ghaem Hospital, Mashhad, Iran. *Iran J Pediatr Soc*. 2010;2:70–74.
12. Saderi H, Roustai MH, Sabahi F, et al. Incidence of enteric adenovirus gastroenteritis in Iranian children. *J Clin Virol*. 2002;24:1–5.
13. Samarbaf-Zadeh A, Pirmoradi R, Shamsizadeh A, et al. Prevalence of adenoviruses 40 and 41 in children less than five years suffering from acute gastroenteritis hospitalized in Ahvaz Abuzar Hospital. *Jundishapur J Microbiol*. 2010;3:48–52.
14. Hamkar R, Yahyapour Y, Noroozi M, et al. Prevalence of rotavirus, adenovirus, and astrovirus infections among patients with acute gastroenteritis in, Northern Iran. *Iran J Public Health*. 2010;39:45–51.
15. Jalilian S, Samarbaf-Zadeh AR, Mozhgani SHR, et al. Relative frequency of norovirus infection in children suffering from gastroenteritis and referred to Aboozar Hospital, Ahvaz, Iran. *Jundishapur J Microbiol.* 2012;5:355–358.
16. Fazeli Z, Baghaie N, Khavarinejad RA, et al. Hospital based study of prevalence and genotyping of Noroviruses and Sapoviruses isolated from children with acute gastroenteritis referred to Masih Daneshvari hospital. *Gastroenterol Hepatol Bed Bench*. 2010;3:91–97.
17. Roodsari SR, Bitajian F, Gachkar L, et al. Detection of Noroviruses Isolated From Children With Acute Gastroenteritis by Rt-PCR in Iran. *Arch Pediatr Infect Dis*. 2013;1:57–60.
18. Romani S, Mohebbi SR, Hosseini SM, et al. Prevalence of norovirus infection in children and adults with acute gastroenteritis, Tehran, Iran, 2008-2009. *Food Environ Virol*. 2012;4:1–5.
19. Romani S, Azimzadeh P, Mohebi SR, et al. Prevalence of sapovirus infection among infant and adult patients with acute gastroenteritis in Tehran, Iran. *Gastroenterol Hepatol Bed Bench*. 2012;5:43–48.
20. Parsa-nahad M, Samarbaf-Zadeh AR, Makvandi M, et al. Relative frequency of sapovirus among children under 5 years of age with acute gastroenteritis at the Aboozar Hospital, Ahvaz, Iran. *Jundishapur J Microbiol*. 2012;5:359–361.
21. Maham S, Marhamati N, Fallah F, et al. Epidemiology of astrovirus infection in young children hospitalized with gastroenteritis in Iran, over a period of seven years, using reverse Transcriptase-polymerase chain reaction (RT-PCR). *J Public Health Epidemiol*. 2013;5:37–42.
22. Mozhgani SHR, Samarbaf-Zadeh AR, Makvandi M, et al. Astrovirus and rotavirus co-infections in children with gastroenteritis who were referred to Ahvaz Aboozar Hospital, Southern Iran. *Jundishapur J Microbiol*. 2012;5:352–354.
23. Mozhgani SHR, Samarbaf-Zadeh AR, Makvandi M, et al.Relative frequency of astrovirus in children suffering from gastroenteritis referred to Aboozar hospital, Ahvaz. *Jundishapur J Microbiol*. 2011;4(suppl 1):S67–S70.
24. Nadji SA, Poos-Ashkan L, Khalilzadeh S, et al. Phylogenetic analysis of human bocavirus isolated from children with acute respiratory illnesses and gastroenteritis in Iran. *Scand J Infect Dis*. 2010;42:598–603.
25. Ghazi F, Ataei Z, Dabirmanesh B. Molecular detection of human parechovirus type 1 in stool samples from children with diarrhea. *Int J Infect Dis*. 2012;16:e673–e676.
26. The Australian Society for Microbiology INC. Viral gastroenteritis. *Microbiol Aust*. 2012;33:48–87.

INDETERMINATE QUANTIFERON-TB GOLD IN-TUBE ASSAY RESULTS IN CHILDREN

POSSIBLE ASSOCIATION WITH PROCEDURAL SPECIMEN COLLECTION

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Abstract: Fifty-six of 182 (31%) children had indeterminate QuantiFERON assays. Indeterminate assays were associated with inpatient status [odds ratios (OR): 11.7, 95% confidence interval 3.9–34.9], but not with age, gender or medical comorbidities. This indicates that indeterminates may be due to specimen handling, and proper procedural training may be necessary to decrease indeterminate QuantiFERON results.

Key Words: interferon-gamma release assay, indeterminate, pediatric; procedural, shaking tubes

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Interferon-gamma release assays (IGRAs) offer enhanced specificity over the tuberculin skin test for the diagnosis of latent tuberculosis infection in some patient groups.[1] The usage of IGRAs as a screening tool may be limited by indeterminate results, which have been found in up to two-thirds of immunocompromised children.[2] However, in immunocompetent children, disparate indeterminate ranges (0–35%) have been reported.[3–5] These indeterminate results have primarily been due to failure of the negative control. The optimal interpretation of a real indeterminate result is unknown and indeterminates can arise for a number of reasons, including a generic lack of T-cell responses from a specific patient or to specimen handling and processing. One of the IGRAs, the QuantiFERON Gold In-Tube (QFT-GIT), requires vigorous shaking of the tubes to ensure the mixing of blood with the antigens in the tubes.[6] As most laboratory draws do not require such shaking, we hypothesized that inadequate training of hospital staff for an infrequently run assay may contribute to indeterminate results.

The goal of this investigation was to explore associations between indeterminate results and specimen collection procedures (using surrogate variables) for the QFT-GIT in a pediatric cohort.

MATERIALS AND METHODS

This was a retrospective study of children (0–18 years of age) in whom QFT-GIT were performed from July 2010 to August 2011 at Texas Children's Hospital (Houston, TX), a tertiary care facility serving a large population of immunocompromised children. Children with indeterminate QFT-GIT were compared with children with determinate IGRAs—positive or negative. None of the children ultimately were treated for TB disease, and no children had QFT-GIT done as part of a public health contact investigation. During the study period, the hospital had a standardized policy for inoculating tubes for QFT-GIT; this was available in the pathology online catalog, which was accessible through the hospital intranet on every computer workstation. These instructions stated that after inoculation of 1 mL blood into the 3 tubes needed for the QFT-GIT, the tubes should be mixed by shaking